Remarks

Examiner maintains that Madden (5,389,378) anticipates (35 USC § 102(b)) claims 1, 2, 6, 8, 10 and 11, based on the abstract and col. 7 line 8 through col. 9 line 62. Also that claims 1, 2, 6, 8, 10-11 and 13 are made obvious (35 USC § 103 (a)) by Desai et al. (?6,074,666?) in view of Madden ('378). [We presume the Desai et al. reference is the same as earlier action, since it is not identified in this action.]

A key point in the referenced abstract is that after reciting a general description of possible lipid components and benzoporphyrin, in line 9 it states "In an additional aspect... ..sized liposomes are described which are storage stable." This implies that to be storage stable a liposomal formulation may require restrictions or additions beyond the basic components. ('378, verified col. 8, line 64ff.)

Another point, not noticed earlier, is the fact that the present invention relies on "synthetic" phospholipids, like DPPC and DPPG to the exclusion of naturally-derived phospholipids, which include the preferred egg phosphatidyl choline, EPC (Madden col. 8, lines 21-26). This restriction, at least, differentiates claim 1 from the work of Madden, Desai et al, etc. Madden specifically prefers EPC over the other listed phospholipids as noted several times in col. 8 of '378. This point is combined with the restriction described below to further confirm the differentiation from the prior art.

Previously amended claim 1 specifically claims a liposomal formulation "which can be safely freeze-dried and reconstituted". Herein lies one of the problems associated with using naturally derived phospholipids, and especially EPC, as the major ingredient for the liposomal formulation of the hydrophobic porphyrin. Madden already states that sugars are known to be needed to permit freeze-drying to dehydration prior to storage. (col. 9 line 8, lines 16-30.) He also states that trehalose and sucrose are most effective. (col. 9 line 14-15.) What the inventors learned from experiments for the present invention, was that monosaccharides, including glucose, do not adequately protect liposomal vesicles from vesicle-fusion/aggregation during freeze-drying and reconstitution nor for lyophilized preparations when naturally derived phospholipids are used to create the liposomes.

Aggregation/fusion of the vesicles occurs very significantly, creating problems in general and especially in dosing for systemically introduced formulations.

Desai et al., as noted, disclose numerous liposomal compositions(formulations), again primarily for hydro-mono benzoporphyrins (BPD), and a wide range of phospholipids. As in Madden, there is a preference for egg phosphatidyl derivative, EPG, a naturally derived phospholipid, and no other differentiation between synthetic and natural phospholipids. In fact there is no identification that the preferred phospholipids are naturally derived. As noted earlier, this is believed to be due to the fact that they used disaccharides and polysaccharides in their formulations, which were freeze-dried. Experiments with the photosensitizers of the present invention and monosaccharides found that the latter failed generally to protect against agglomeration/aggregation/fusion of the vesicles when EPC or naturally derived phospholipids were a phospholipid forming the liposomes.

Since both '378 and '666 teach that EPC or EPG is a preferred phospholipid, and neither teaches anything about differentiating between naturally derived phospholipids and synthetic phospholipids other than this preference, these patents alone and together cannot anticipate nor make obvious the present invention. At best they do not understand there can be a difference between synthetic and natural phospholipid liposomes during freeze-drying and reconstitution. (See e.g. '666, col. 5 lines 60-66, listing egg phosphatidyl choline and soy phosphatidyl choline with DPPC and DMPC) More directly they teach away from the present invention in that they pronounce that a natural phospholipids, EPC/EPG, (see also '666, col. 6, line 3-5) is their preferred embodiment, while the present invention is based on synthetic phospholipids being a necessary (as per amended claim 1) component of the liposomal formulations claimed herein.

It is agreed with the examiner that the references, '378, '666 and GB2146525A, all mention components identified in claim 1 and some subsequent claims. The point that seems to be missing is that to achieve stable vesicles which can withstand freeze-drying and reconstitution using monosaccharides, such as glucose, with non-polar di- and tetra-hydroporphyrins requires that the vesicles employ a synthetic phospholipid such as DPPC or DMPC, DPPG or DMPG. All the examples presented from the start have included only known synthetic phospholipids. The prior art references employ, and even state preferences

for, naturally derived phospholipids such as EPC or EPG. (see e.g. '666 col. 7 lines 16-19; '378 col. 8 lines 21-26). Their teachings direct one away from the formulations found and claimed in the present invention or at the least do not instruct why a preferred composition in their patents should not be stable within the restricted formulation area covered by the present invention.

With these remarks and exposition of terms within the previously amended claims it is believed that the disclosure is now in condition for further analysis and allowance. Reconsideration is respectfully requested. An early and favorable response is earnestly solicited. Thank you.

Respectfully submitted,

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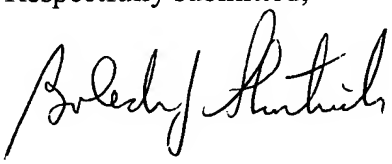

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